DP Barcode: 450645 MRID No.: 50451002

DATA EVALUATION RECORD
CHRONIC (REPEATED DOSE) TOXICITY TEST WITH THE HONEY BEE
NON-GUIDELINE

1. **CHEMICAL:** Ipconazole PC Code No.: 125618

2. **TEST MATERIAL:** Ipconazole (technical material) Purity: 96.7% w/w (as total Ipconazole), 89.7% w/w (as Ipconazole cc),and 7.0% w/w (as Ipconazole ct)

3. **CITATION**

Authors:	Patnaude, M. R.
Title:	Ipconazole: Honey Bee (*Apis mellifera*) Larval Toxicity Test, Repeat Exposure
Study Completion Date:	November 21, 2017
Laboratory:	Smithers Viscient
Sponsor:	Kureha Corporation
Study No.:	11106.6109
MRID:	50451002
DP Barcode:	450645

4. **REVIEWED BY:** Holly Dimig, Junior Staff Scientist, CDM/CSS-Dynamac JV

Signature: Holly Dimig **Date:** 04/30/2019

APPROVED BY: Adrian Graff, Environmental Scientist, CDM/CSS-Dynamac JV

Signature: Adrian T. Graff **Date:** 05/13/2019

5. **APPROVED BY:** Holly Rogers, Biologist, EPA/OPP/EFED/ERB5

Signature: Holly Rogers Digitally signed by HOLLY ROGERS Date: 2020.05.04 12:27:34 -04'00' **Date:** 05/04/2020

APPROVED BY: Hannah Yingling, Biologist, USEPAEPA/OPP/EFED/ERB5

Signature: Hannah B. Yingling **Date:** 04/28/2020

This Data Evaluation Record may have been altered by the Environmental Fate and Effects Division subsequent to signing by CDM/CSS-Dynamac JV personnel. The CDM/CSS-Dynamac Joint Venture role does not include establishing Agency policies.

6. STUDY PARAMETERS:

Test Species and strain: Larval Honey bees, (*Apis mellifera*)
Age of Test Organisms at Test Initiation: 1st instar larvae, ≤24-hours old.
Exposure Duration: 22 days

7. CONCLUSIONS:

Individual synchronized honey bee (*Apis mellifera*) larvae (first instar) were exposed *in vitro* to Ipconazole (technical material) on Days 3 (D3) through Day 6 (D6) of the study at the nominal diet concentrations and nominal cumulative doses reported in the table below. The study author calculated the mean-measured diet concentrations, and applied the analytical recoveries to the cumulative doses to obtain the measured cumulative dietary doses. The reviewer divided those cumulative doses by the number of days of exposure (4) to obtain the measured daily doses of total Ipconazole. Concentrations and doses are summarized in the table below:

Nominal Diet Concentrations (µg ai/g diet)	Mean Measured Concentrations (µg ai/g diet)	Nominal Cumulative Doses (µg ai/larva)	Measured Cumulative Dietary Doses (µg ai/larva)	Measured Daily Dietary Doses (µg ai/larva/day)
8.8	8.8	1.4	1.4	0.35
25	25	4.0	4.0	1.0
75	68	12	11	2.8
210	210	34	34	8.5
630	630	100	100	25.0

Larvae used in the study were provided by Wood's Beekeeping Supply, Lincoln, Rhode Island. Dimethoate was tested as a reference toxicant at a nominal dose of 7.4 µg ai/larva. All groups consisted of 36 larvae per treatment group, placed within 48-well cell culture plates.

On Day 8, cumulative larval mortality was 0 and 3% in the negative and solvent controls, respectively, compared to mortality ranging from 0 to 100% in the treatment groups. On day 15, cumulative mortality averaged 3 and 11% in the negative and solvent controls, respectively, compared to mortality ranging from 3 to 100% in the treatment groups. On Day 22, the adult emergence rate was 94 and 86% in the negative and solvent controls, respectively, compared to emergence ranging from 0 to 97% in the treatment groups.

Weight was not recorded for organisms in the highest test level due to 100% mortality among organisms in this treatment level. Average weight was 0.104 and 0.103 g in the negative and solvent control groups, respectively, and ranged from 0.100 to 0.103 g in the treatment groups.

On Day 8, no uneaten diet was reported for any of the surviving larvae.

On Days 6 and 7, two, one, zero, nine, and two replicates were observed to be small in size in the 0.35, 1.0, 2.8, 8.5, and 25.0 µg ai/larva/day treatment groups, respectively, compared to one and seven replicates observed to be small in size in the negative and solvent controls, respectively.

Based on these results, the most sensitive endpoint was percent emergence, and the 22-day NOAEC and EC_{50} were determined to be 210 and 313 µg ai/g diet, respectively, corresponding to a NOAEL and ED_{50} of 8.5 and 13 µg ai/larva/day, respectively. Larval mortality, day 15 mortality, and adult emergence were significantly affected at the highest treatment level of 630 µg ai/g diet (or 25 µg ai/larva/day on a daily dietary dose basis). Emerged bee weight was unaffected.

The study **is scientifically sound** and is consistent with the OECD Guidance Document for measuring chronic (repeat dose) toxicity to honeybee larvae. The study is classified as **acceptable**.

	Mortality (Day 8)	**Mortality (Day 15)**	**Adult Emergence**	**Weight**
Diet Concentration (µg ai/g diet)	LC_{50}: 353 95% CI: 333 to 375 Slope: N/A NOAEC: 210 LOAEC: 630	LC_{50}: 332 95% CI: 298 to 370 Slope: N/A NOAEC: 210 LOAEC: 630	EC_{50}: 313 95% CI: 275 to 357 Slope: N/A NOAEC: 210 LOAEC: 630	IC_{50}: >210 95% CI: N/A Slope: N/A NOAEC: 210 LOAEC: >210
Dietary Dose (µg ai/larva/day)	LD_{50}: 14 95% CI: 13 to 15 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	LD_{50}: 13 95% CI: 12 to 15 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	ED_{50}: 13 95% CI: 11 to 14 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	ID_{50}: >8.5 95% CI: N/A Slope: N/A NOAEL: 8.5 LOAEL: >8.5

8. ADEQUACY OF THE STUDY:

A. Classification: This study **is scientifically sound** and is classified as a**cceptable**.

B. Rationale: There were no major deviations or deficiencies in this study and all validity criteria for the OECD guideline used were met in this study:

1. Cumulative larval mortality across all control replicates from D3 to D8 was ≤15%.

2. Adult emergence across all control replicates on D22 was ≥ 70%.
3. Cumulative larval mortality in the positive control of Dimethoate on D8 was ≥ 50%.

C. Reparability: N/A

9. GUIDELINE DEVIATIONS: Procedures used in this study followed those described in the Smithers Viscient protocol entitled "Ipconazole: 22-Day Survival of Honey Bee Larvae, *Apis mellifera* L., during an *In Vitro* Exposure". The procedures used in this study are based on the OECD Guideline 239 dated 15 July 2016, procedures discussed in Protocol for the *in vitro* rearing of honey bee (*Apis mellifera* L.) workers (Schmehl, *et. al*., 2016), and input from the U.S. EPA. The following deviations from OECD 239 were noted by the reviewer:

1) The study author reported individual bee data for days 3 – 8 and day 15, but only reported group data for day 22. According to the EPA's Honeybee Toxicity Testing Frequently Asked Questions – August 16, 2018, the individual bee is considered the replicate based on the dose being administered to each well which only contains a single individual. While the study author defined the replicate in the same manner as the EPA, this was not reflected in the raw data for bee weight and emergence.

2) Royal jelly diet preparation ratios of Diets A, B, and C are based on modifications from Schmehl *et al.* (2016) and diet compositions for A and B deviated from OECD guidance.

3) The shape of the grafted larvae at transfer was not reported. OECD recommends that newly hatched larvae are selected that have not yet formed a "C" shape.

4) Random or impartial assignment of bees to test groups was not reported in the study report; however, the randomization is stated as part of the guiding study protocol (Appendix 1, pg. 53-54).

5) The temperatures in two of the three bee development stages were slightly out of the suggested ranges. OECD allows temporary deviations however they should not last more than 30 minutes every 24 hours.

Days 1 to 8: 33-34 °C (recommended 34-35 °C)
Days 7 to 15: 33-34 °C (recommended 34-35 °C)

6) The relative humidity in the pupal phase was not within the suggested ranges. OECD allows temporary deviations however they should not last more than 30 minutes every 24 hours.

Days 7 to 15: 51 to 72% (recommended 80 ± 5%)

7) The physicochemical properties of Ipconazole technical were not reported.

These deviations **do not** affect the study.

10. SUBMISSION PURPOSE: This study was conducted to determine the effects of Ipconazole (technical material) on honey bee (*Apis mellifera*) larva following chronic oral exposure for the purpose of chemical re-registration.

11. MATERIALS AND METHODS:

A. Test Material:	Ipconazole (technical material)
Description:	White powder
Lot No./Batch No.:	89010
Purity:	96.7% w/w (as total ipconazole), 89.7% w/w (as ipconazole cc), and 7.0% w/w (as ipconazole ct)
CAS Number:	125225-28-7
Stability of compound under test conditions:	Analytical measurements of total Ipconazole in the royal jelly larval diet demonstrated that the mean test item concentrations were recovered at rates ranging from 90 to 100% of nominal.
Storage conditions of test chemical:	Stored at room temperature in a dark, ventilated cabinet in the original container.

Range finding test yes/no (if yes, describe): Yes, a non-GLP preliminary test similar to the definitive test was initiated at Smithers Viscient on May 12, 2017 at nominal concentrations of 0.10, 1.0, 10, and 100 µg ai/larva, including a negative control and a solvent (acetone) control. One cell plate, containing 24 larvae per treatment and control was established. Day 3-8 larval survival was 92 and 83% in the negative and solvent controls, respectively, compared to mortality ranging from 4 to 92% in the treatment groups, and days 3-22 adult emergence was 83% in both the negative and solvent controls compared to emergence ranging from 0 to 83% in the treatment groups (emergence was 0% in the highest dosed test group). Based on these findings and in consultation with the Study Sponsor, nominal Ipconazole levels of 1.4, 4.0, 12, 34, and 100 µg ai/larva, equivalent to 8.8, 25, 75, 210, and 630 µg ai/g diet, respectively, a negative control, and a solvent (acetone) control were selected for the definitive exposure.

Physicochemical properties of Ipconazole used in solubility/homogeneity study.

Parameter	Values	Comments
Molecular Weight	Not reported	
Water solubility at 20°C (mg/L)	Not reported	See reviewer's comments
Vapor pressure (torr, at 25°C)	Not reported	
Mean organic carbon partition coefficient K_{oc} (L/kg_{oc})	Not reported	
Log octanol-water partition coefficient Log K_{ow}	Not reported	

B. Test Organisms

Guideline Criteria	Reported Information	Comments
Species	Honey bee (*A. mellifera*) identified as Italian hybrids, a mixture of the original subspecies *A. mellifera ligustica* and unidentified subspecies.	_____ *OECD recommends European honey bee (Apis mellifera)*
Age at beginning of test Worker bees of uniform age.	First instar larvae, ≤24 hours old.	_____ *OECD recommends that on D1 of study, first instar (L1) synchronized larvae (i.e., larvae of the same age) are taken from comb of three colonies.*
Source	Wood's Beekeeping Supply, Lincoln, Rhode Island, from 3 or more hives.	_____ *OECD recommends larvae are collected from three different colonies.*
Were bees from disease-free colonies?	Not reported. The larvae were obtained from hives that had not been previously exposed to any chemical treatments within 4 weeks of test initiation.	_____ *OECD recommends that colonies used to obtain larvae should be adequately fed, health (i.e., as far as disease- and parasite-free), with a known history and physiological status.*

Guideline Criteria	Reported Information	Comments
Were bees kept in conditions conforming to proper cultural practices?	Not reported, but bees were obtained from a beekeeping supplier.	

C. Test System

Guideline Criteria	Reported Information	Comments
Test Chambers	Larvae were reared in sterile, 48-well cell culture plates (1.6 mL/well, Corning® Costar® 3548) containing a plastic queen cup grafting cell (Mann Lake, QC-110) in 32 wells during acclimation and in 18 wells during exposure. The pupation plates were sterile, 24-well cell culture plates (3.4 mL/well, Corning® Costar® 3526) each containing two layers of sterilized dust-free Kimwipes®.	*OECD recommends 48-well plate with each well containing a crystal polystyrene grafting cell.*
Temperature during exposure	Days 1 to 8: 33 to 34 °C Days 7 to 15: 33 to 34 °C Days 15 to 22: 33 to 34 °C The larvae, in their cell plates, were kept inside a plastic container in the same incubator used for the acclimation phase. Larvae, upon transfer to the pupal plates, were maintained within a different incubator and monitored continuously.	*OECD recommends incubator at 34 – 35°C. Deviations may occur but temperature should not be lower than 23°C or higher than 40°C; deviations not last more than 15 minutes once every 24 hrs.*
Relative humidity during exposure	Days 1 to 8: 90 to 98% Days 7 to 15: 51 to 72% Days 15 to 22: 60 to 70%	*OECD recommends use of K_2SO_4 to maintain water saturated atmosphere.*

Guideline Criteria	Reported Information	Comments
	The perimeter wells within each plate not containing larvae were partially filled with deionized water to assist in maintaining a water saturated atmosphere. Continuous monitoring was utilized.	

Guideline Criteria	Reported Information	Comments
Lighting	Constant darkness except for approximately 30 minutes each day during observations and renewal of the diet.	_____ *OECD recommends that plates should be maintained in darkness.*

Guideline Criteria	Reported Information	Comments
Feeding	Each larva was fed for 6 days (except on Day 2) with a standardized amount of an artificial diet of 20 µL untreated **Diet A** on Day 1, not fed on Day 2, 20 µL treated/untreated **Diet B** on Day 3, and 30, 40, and 50 µL of the appropriately treated **Diet C** on Days 4, 5, and 6 respectively. Diet A[a]: 44% weight of royal jelly + 56% weight of an aqueous solution containing 2% weight of yeast extract, 9% weight of glucose + 9% weight of fructose. Diet B[a]: 43% weight of royal jelly + 57% weight of an aqueous solution containing 2% weight of yeast extract, 11% weight of glucose + 11% weight of fructose. Diet C[a]: 50% weight of royal jelly + 50% weight of an aqueous solution containing 4% weight of yeast extract, 18% weight of glucose + 18% weight of fructose. [a] calculated by the reviewer based on diet components provided on pages 17 and 53 of the study report.	The study author reported that royal jelly diet preparation ratios are based on modifications from Schmehl *et al* (2016). _____ *OECD recommends that all larvae are fed once a day. Volume of diet is adjusted each day. Additional food should be added to the cell even if previous allocation has not been totally consumed. Presence of uneaten food at termination of test should be reported.* *OECD recommends:* *Diet A (D1): 50% weight of fresh royal jelly + 50% weight of an aqueous solution containing 2% weight of yeast extract, 12% weight of glucose and 12% weight of fructose* *Diet B (D3): 50% weight of fresh royal jelly + 50% weight of an aqueous solution containing 3% weight of yeast extract, 15% weight of glucose and 15% weight of fructose.* . *Diet C (from D4 to D6): 50% weight of fresh royal jelly + 50% weight of an aqueous solution containing 4% weight of yeast extract, 18% weight of glucose and 18% weight of fructose.*

D. Test Design

Guideline Criteria	Reported Information	Comments
Nominal test applications	Diet Concentrations: 0 (negative and solvent controls), 8.8, 25, 75, 210, and 630 µg ai/g diet Cumulative Doses: 0 (negative and solvent controls), 1.4, 4.0, 12, 34, and 100 µg ai/larva	*OECD recommends 5 treatments of increasing test concentrations. Alternatively, when a limit test is performed, a single dose of 100 µg ai/larva or the maximum achievable solubility (whichever is lower).*
Measured test applications	Diet Concentrations as Total Ipconazole: <1.3 (<MDL, controls), 8.8, 25, 68, 210, and 630 µg ai/g diet Daily Dietary Doses[a] as Total Ipconazole: 0 (controls), 0.35, 1.0, 2.8, 8.5, and 25.0 µg ai/larva/day [a] Calculated by the reviewer.	
Number of bees exposed per dosage level	36 larvae per test group The replicate unit was the individual larva/bee since they were reared in an individual cell.	*OECD recommends minimum of 12 larvae from each of 3 colonies allocated on the same plate to each treatment, i.e., minimum of 36 larvae per treatment.*
Other experimental design information	The queen from three or more hives was isolated on a single frame for one day to provide known-aged eggs and subsequent larvae. The frames were delivered to Smithers Viscient so that ≤24-hour old larvae were removed for testing.	*OECD recommends that newly hatched larvae are selected that have not yet formed a "C" shape and randomizing the allocation of larvae into the plates for each colony. On Day 1, larva is deposited in cell containing 20 µL diet.*

Guideline Criteria	Reported Information	Comments
	Larvae were fed 20 µL of untreated Diet A on the day of transfer into the cell plates. The shape of the grafted larvae at transfer was not reported. Excess larvae were collected. A 0.15 g ai/mL primary stock solution was prepared by bringing 7.7760 g of Ipconazole (7.5194 g as active ingredient to adjust for purity) to a volume of 50 mL with acetone. Additional stock solutions were prepared using a dilution scheme; the primary stock solution was used to prepare the dosing stock solutions. The solvent control diet contained an equivalent amount of untreated acetone (0.42%) as each treated diet. Untreated diet was used for the negative control.	

Guideline Criteria	Reported Information	Comments
Bees randomly or impartially assigned to test groups	Not reported in study report but is stated as part of the guiding study protocol (Appendix 1, pg. 53-54).	_____ *OECD recommends that each group of a minimum of 12 larvae from each of the three colonies is considered a replicate for a given treatment level and identified as such on the microplate.*
Control	Untreated diet. 36 negative control larvae.	_____ *OECD recommends 12 larvae x 3 colonies=36 larvae minimum and that control mortality from D4 to D7 should be ≤15%.*
Solvent control	Untreated diet with 0.42% acetone. 36 solvent control larvae.	_____ *OECD recommends maximum of 5%.*
Reference Toxicant	Dimethoate, tested at a nominal dose of 7.4 µg ai/larva. 36 reference larvae.	_____ *OECD recommends technical grade dimethoate at dose of 8.8 ± 0.5 µg a.i./larva. Mortality should be ≥50% at D7 for toxic reference.*
Total observation period and frequency of interim observations	The health of the larvae was observed and recorded daily. Diet in the wells was observed on D7 and D8, and the number of larvae transferred to pupal plates was recorded. Survival of pupae was first checked on D15. Larvae that failed to develop into pupae by D15 were classified as dead. Starting on D15, the number of emerged	_____ *OECD recommends that following chemical exposure on D4, mortalities are checked at time of feeding on D5, D6 and D7 (test termination). Other observations including presence of uneaten food on D7 should be qualitatively reported.*

Guideline Criteria	Reported Information	Comments
	adults each day was recorded. At the time of emergence, each adult bee, observed to be fully sclerotized with developed wings, was removed from the well plate and individually weighed.	

12. REPORTED RESULTS:

Guideline Criteria	Reported Information
Quality assurance and GLP compliance statements were included in the report?	Yes. The data and report were produced and compiled in accordance with all pertinent U.S. Environmental Protection Agency (EPA) Good Laboratory Practice Standards (GLPs) as set forth under the Federal Insecticide, Fungicide, and Rodenticide Act (1989) and as accepted by the OECD Principles of Good Laboratory Practice (1998) with the following exceptions: 1) Routine water and royal jelly diet contaminant screening analyses for pesticides, PCBs, toxic metals, and antibiotics was conducted using standard U.S. EPA procedures by GeoLabs, Inc., Braintree, Massachusetts and the U.S. Department of Agriculture, Gastonia, North Carolina, and are considered facility records under Smithers Viscient's Standard Operating Procedures and 2) The reference toxicant, Dimethoate, was purchased from a commercial supplier and was not characterized in accordance with GLP Standards.
Observed adverse effects on bees at respective dosages	The study author determined a significant reduction in larval survival among honey bees exposed to levels >8.5 µg ai/larva/day compared to the negative control. On Day 8, there was 100% mortality among larvae in the 25.0 µg ai/larva/day treatment level and therefore, no pupae were present in the 25.0 µg ai/larva/day treatment. This treatment level was excluded from statistical analysis of the pupal survival endpoint.

Guideline Criteria	Reported Information
	Weight was not recorded for organisms in the 25.0 µg ai/larva/day treatment due to 100% mortality among organisms in this treatment level. On Day 8, no uneaten diet was reported for any of the surviving larvae. On Days 6 and 7, two, one, zero, nine, and two replicates were observed to be small in size in the 0.35, 1.0, 2.8, 8.5, and 25.0 µg ai/larva/day treatment groups compared to one and seven replicates observed to be small in size in the negative and solvent controls, respectively.
Control and Solvent Control Mortality	<u>D8 Cumulative Mortality</u> Negative control: 0% Solvent control: 3% <u>D15 Cumulative Mortality</u> Negative Control: 3% Solvent control: 11% <u>D22 Cumulative Mortality</u> Negative control: 6% Solvent control: 14%
Were raw data included?	Raw data for D1-D8 and for D15 were included. Otherwise, summary tables were provided.
Analytical Analysis?	Yes, conducted in-house at Smithers Viscient with liquid chromatography with tandem mass spectrometry detection (LC-MS/MS).

Mortality and Observations:

On Day 8, cumulative larval mortality was 0 and 3% in the negative and solvent controls,

respectively, compared to mortality ranging from 0 to 100% in the treatment groups (Table 1). On Day 8, there was 100% mortality among larvae in the 25.0 µg ai/larva/day treatment level and therefore, no pupae were present in the 25.0 µg ai/larva/day treatment. By Day 15, cumulative mortality averaged 3 and 11% in the negative and solvent controls, respectively, compared to mortality ranging from 3 to 100% in the treatment groups (Table 2). On Day 22, the adult emergence rate was 94 and 86% in the negative and solvent controls, respectively, compared to emergence ranging from 0 to 97% in the treatment groups (Table 2).

The study author determined a statistically significant reduction in larval survival among honey bees exposed to levels >8.5 µg ai/larva/day compared to the negative control. This treatment level was excluded from the study author's statistical analysis of the pupal survival endpoint.

Weight was not recorded for organisms in the 25.0 µg ai/larva/day treatment due to 100% mortality among organisms in this treatment level.

On Day 8, no uneaten diet was reported for any of the surviving larvae.

On Days 6 and 7, two, one, zero, nine, and two replicates were observed to be small in size in the 0.35, 1.0, 2.8, 8.5, and 25.0 µg ai/larva/day treatment groups compared to one and seven replicates observed to be small in size in the negative and solvent controls, respectively.

Table 1. Cumulative honey bee larval mortality data after repeated dietary exposure (dose) of Ipconazole[a].

Mean Measured Concentration (Measured Daily Dietary Dose)	Number Exposed	Day 4 % Mortality	Day 5 % Mortality	Day 6 % Mortality	Day 7 % Mortality	Day 8 % Mortality
Negative Control	36	0	0	0	0	0
Solvent Control	36	0	0	3	3	3
8.8 µg ai/g diet (0.35 µg ai/larva/day)	36	0	0	0	0	0
25 µg ai/g diet (1.0 µg ai/larva/day)	36	0	0	0	0	3
68 µg ai/g diet (2.8 µg ai/larva/day)	36	0	0	0	0	0
210 µg ai/g diet (8.5 µg ai/larva/day)	36	0	0	0	0	0
630 µg ai/g diet (25.0 µg ai/larva/day)	36	0	19	94	97	100
Nominal Dose Dimethoate 7.4 µg ai/larva	36	19	42	75	78	81

[a] Data based on % survival data obtained from Table 5 on p. 39 of the MRID.

Table 2. Cumulative honey bee pupal mortality, adult emergence, and weight at emergence data after repeated dietary exposure (dose) of Ipconazole.

Mean Measured Concentration (Measured Daily Dietary Dose)	Number Exposed	Day 15 % Mortality[a]	Day 22 % Mortality[b]	Day 22 Adult % Emergence[b]	Mean Adult Weight at Emergence (g), Mean (SD)[c]
Negative Control	36	3	6	94	0.1044 (0.0103)
Solvent Control	36	11	14	86	0.1031 (0.0118)
8.8 µg ai/g diet (0.35 µg ai/larva/day)	36	6	6	94	0.1014 (0.0142)
25 µg ai/g diet (1.0 µg ai/larva/day)	36	3	3	97	0.1028 (0.0118)
68 µg ai/g diet (2.8 µg ai/larva/day)	36	3	8	92	0.1001 (0.0114)
210 µg ai/g diet (8.5 µg ai/larva/day)	36	11	14	86	0.1008 (0.0153)
630 µg ai/g diet (25.0 µg ai/larva/day)	36	100	100	0	N/A

[a] Calculated by the reviewer based on replicate data for cumulative # dead obtained from p. 129-135 of the MRID.
[b] Data obtained from Table 6 on p. 40 of the MRID.
[c] Data obtained from Table 7 on p. 41 of the MRID.
N/A Not applicable

Reported Statistics:

CETIS Version 1.8 (2013) was used to perform all statistical analysis.

Fisher's Exact Test indicated that the day 3 to 8 larval survival data for the negative control and solvent control data were not significantly different. Therefore, treatment data were compared to the negative control data to define treatment effects.

The treatment data were tested for normality and homogeneity of variance using the appropriate qualifying test. LOAEL/LOAEC and NOAEL/NOAEC values for larval survival, pupal survival, and adult percent emergence were determined by Fisher's Exact Test with Bonferroni-Holm's Adjustment. LOAEL/LOAEC and NOAEL/LOAEC values for weight at adult emergence were determined by Dunn's Test with Bonferroni-Holm's Adjustment. All comparisons for determination of a NOAEL/LOAEL and NOAEC/LOAEC were made at ≥ 95% level of certainty ($p \leq 0.05$) and compared on a per replicate basis. The replicate unit was the individual larva/bee since they were reared in an individual cell.

The model selected within CETIS to estimate LD_x/LC_x values was determined by the data. If ≥50% mortality was observed, then the LD_{50}/LC_{50} and 95% confidence intervals were calculated. If no treatment level tested resulted in ≥50% mortality, then the LD_{50}/LC_{50} values were empirically estimated to be greater than the highest dose and concentration tested, respectively.

If ≥50% reduction in adult percent emergence or weight was observed, then the appropriate statistical model within CETIS Version 1.8 was used to determine the ED_{50}/EC_{50} values. If no treatment level tested resulted in ≥50% reduction in the endpoint, the ED_{50}/EC_{50} values were empirically estimated to be greater than the highest dose and concentration tested, respectively.

On Day 8, there was 100% mortality among larvae in the 100 µg ai/larva (25.0 µg ai/larva/day) treatment level and therefore, no pupae were present. This treatment level was excluded from statistical analysis of the pupal survival endpoint.

The study author reported the following, based on the mean measured diet concentrations and measured cumulative doses:

<u>Larval Survival (Day 3 to 8)</u>
LD_{50}: 57 µg ai/larva 95% C.I.: (53 - 60)
NOAEL: 34 µg ai/larva
LOAEL: 100 µg ai/larva

LC_{50}: 350 µg ai/g diet 95% C.I.: (330 - 370)
NOAEC: 210 µg ai/g diet
LOAEC: 630 µg ai/g diet

<u>Pupal Survival (Day 8 to 22)</u>
Day LD_{50}: >34 µg ai/larva 95% C.I.: N/A
NOAEL: 34 µg ai/larva
LOAEL: >34 µg ai/larva

Day LC_{50}: >210 µg ai/g diet 95% C.I.: N/A
NOAEC: 210 µg ai/g diet
LOAEC: >210 µg ai/g diet

<u>Adult Emergence</u>
ED_{50}: 50 µg ai/larva 95% C.I.: (44 – 57)
NOAEL: 34 µg ai/larva
LOAEL: >34 µg ai/larva

EC_{50}: 310 µg ai/g diet	95% C.I.: (280 – 360)
NOAEC: 210 µg ai/g diet	
LOAEC: >210 µg ai/g diet	

Adult Weight at Emergence

22-Day ID_{50}: >34 µg ai/larva	95% C.I.: N/A
NOAEL: 34 µg ai/larva	
LOAEL: >34 µg ai/larva	

22-Day IC_{50}: >210 µg ai/g diet	95% C.I.: N/A
NOAEC: 210 µg ai/g diet	
LOAEC: >210 µg ai/g diet	

Reviewer's Statistical Analysis:

Statistical method: Larval mortality, day 15 mortality, adult emergence, and emerged bee weight data were analyzed using CETIS statistical software version 1.9.5.3 with database backend settings implemented by EFED on 7/25/17. Four test records were established in CETIS named "50451002 dc" and "50451002 dd" for measured diet concentrations and measured daily dietary doses to capture mortality (day 8 and day 15) endpoint data and "50451002 dc2" and "50451002 dd2" to capture adult emergence and bee weight endpoint data, as replicate data were not provided for these endpoints.

Negative and solvent control data for day 15 mortality and larval mortality were compared using an Equal Variance t Two-Sample test ($\alpha = 0.05$) and no statistically significant differences were noted. Negative and solvent control data for emergence were compared using a Fisher Exact test ($\alpha = 0.05$) with no significant difference noted. Bee weight negative and solvent control data could not be compared. However, the bee weights were very similar in the controls. All further hypothesis testing was conducted comparing treatment data to negative control data only.

Treatment data for day 15 mortality, larval mortality, and adult emergence were compared to negative control data using a Fisher Exact/Bonferroni-Holm test ($\alpha = 0.05$). Bee weight data were evaluated using a Jonckheere-Terpstra Step-Down test ($\alpha = 0.05$), as a Mann-Whitney U Two-Sample test could not be used.

$LC/LD/EC/ED_{50}$ values for larval mortality, day 15 mortality, and adult emergence were estimated using the Trimmed or Untrimmed Spearman-Kärber method, because linear regression was not appropriate for the data (either the method couldn't be performed or there weren't calculable 95 confidence limits). Due to a lack of bee weight data for the highest treatment level as a result of 100% mortality and an absence of significant effects at any treatment level, the IC/ID_{50} values for bee weight were empirically estimated as greater than the second highest concentration or dose tested.

	Mortality (Day 8)	Mortality (Day 15)	Adult Emergence	Weight
Diet Concentration (µg ai/g diet)	LC_{50}: 353 95% CI: 333 to 375 Slope: N/A NOAEC: 210 LOAEC: 630	LC_{50}: 332 95% CI: 298 to 370 Slope: N/A NOAEC: 210 LOAEC: 630	EC_{50}: 313 95% CI: 275 to 357 Slope: N/A NOAEC: 210 LOAEC: 630	IC_{50}: >210 95% CI: N/A Slope: N/A NOAEC: 210 LOAEC: >210
Dietary Dose (µg ai/larva/day)	LD_{50}: 14 95% CI: 13 to 15 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	LD_{50}: 13 95% CI: 12 to 15 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	ED_{50}: 13 95% CI: 11 to 14 Slope: N/A NOAEL: 8.5 LOAEL: 25.0	ID_{50}: >8.5 95% CI: N/A Slope: N/A NOAEL: 8.5 LOAEL: >8.5

13. REVIEWER'S COMMENTS:

The reviewer's and study author's findings based on the diet concentrations were in complete agreement over the bee weight endpoint toxicity values and in general agreement with the larval mortality and adult emergence endpoint toxicity values. The NOAEC values for emergence were in agreement, while the LOAEC values were not because the study author excluded the highest test level from the determination of the LOAEC. The reviewer analyzed day 15 mortality whereas the study author instead analyzed day 22 survival, so these endpoint toxicity values were not comparable. The study author reported in terms of measured cumulative doses and the reviewer reported in terms of measured daily dietary doses, but the results based on the diet concentrations were sufficient for comparative purposes. The reviewer's findings are presented in the Conclusions and Reviewer's Conclusions sections of this DER.

All three validity criteria were met for the OECD draft guidance followed:

1. Cumulative larval mortality across all control replicates from D3 to D8 was ≤15%.
2. Adult emergence across all control replicates on D22 was ≥ 70%.
3. Cumulative larval mortality in the positive control of Dimethoate on D8 was ≥ 50%.

A non-GLP diet trial was conducted under Smithers Viscient Study Number 11106.6107. The objective of the trial was to determine the solubility, homogeneity, and 4-day stability of Ipconazole in royal jelly diet at relevant dose rates. Based on the results of this trial, it was concluded that reproducible diet concentrations equivalent to 100 µg ai/larva could be prepared in royal jelly diet for this testing. In addition, the results demonstrated that Ipconazole was stable in the diets for up to 4 days. The functionally soluble portion of the sucrose diet dosed at the equivalency of 100 µg ai/bee/day yielded mean recoveries of 32% in the 50% sucrose solution diet and 22% in the 67% sucrose solution diet. These represent the maximum achievable concentration (equivalent to 32 µg ai/bee/day) in 50% sucrose solution diet during definitive testing. Based on the higher recoveries noted in 50% sucrose solution diet, 50% sucrose solution

diet was used to prepare the diets in the definitive test.

The in-life phase of this study was conducted from June 7 to June 28, 2017.

14. REVIEWER'S CONCLUSIONS:

Based on these results, the most sensitive endpoint was percent emergence, and the 22-day NOAEC and EC_{50} were determined to be 210 and 313 µg ai/g diet, respectively, corresponding to a NOAEL and ED_{50} of 8.5 and 13 µg ai/larva/day, respectively. Larval mortality, day 15 mortality, and adult emergence were significantly affected at the highest treatment level of 630 µg ai/g diet (or 25 µg ai/larva/day on a daily dietary dose basis). Emerged bee weight was unaffected.

15. REFERENCES:

Ives, M., 2013. CETIS, Comprehensive Environmental Toxicity Information System™, User's Guide. Tidepool Scientific Software, McKinleyville, California.

Schmehl. D.R., H.V.V. Tomé, A. N. Morttensen, G. Ferreira Martins and J. D. Ellis, 2016. Protocol for the in vitro rearing of honey bee (*Apis mellifera* L.) workers. Journal of Apicultural Research. Volume 55, No. 2. 113 - 129 pp.

All other references were standard guidelines or methodologies.

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24
Sample ID:	12-5729-0907	**Code:**	50451002 dc	**Project:**	Fungicide
Sample Date:	09 Jun-17	**Material:**	Ipconazole	**Source:**	Kureha Corporation
Receipt Date:	28 Jun-17	**CAS (PC):**		**Station:**	
Sample Age:	n/a	**Client:**	CDM Smith		

125618 50451002, mean-measured diet concentrations (ug ai/g diet), larval and d15 mortality data, stats performed by A. Graff

SIngle Comparison Summary

Analysis ID	Endpoint	Comparison Method	P-Value	Comparison Result	S
02-8790-3949	Day 15 Mortality	Equal Variance t Two-Sample Test	0.1689	Solvent Blank passed day 15 mortality	1
01-4910-8732	Larval Mortality	Equal Variance t Two-Sample Test	0.3208	Solvent Blank passed larval mortality	1

Multiple Comparison Summary

Analysis ID	Endpoint	Comparison Method	✓	NOEL	LOEL	TOEL	TU	PMSD	S
07-6727-4899	Day 15 Mortality	Fisher Exact/Bonferroni-Holm Test	✓	210	630	363.7		n/a	1
20-7378-5920	Larval Mortality	Fisher Exact/Bonferroni-Holm Test	✓	210	630	363.7		n/a	1

Point Estimate Summary

Analysis ID	Endpoint	Point Estimate Method	✓	Level	µg ai/g	95% LCL	95% UCL	TU	S
09-9507-1814	Day 15 Mortality	Trimmed Spearman-Kärber	✓	LC50	332	298	370		1
18-7051-1920	Larval Mortality	Spearman-Kärber		LC50	353	333	375		1

Day 15 Mortality Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	36	0.111	0.003	0.219	0.000	1.000	0.053	0.319	286.85%	0.00%
0	N	36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
8.8		36	0.056	0.000	0.134	0.000	1.000	0.039	0.232	418.16%	-6.25%
25		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
68		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
210		36	0.111	0.003	0.219	0.000	1.000	0.053	0.319	286.85%	0.00%
630		36	1.000	1.000	1.000	1.000	1.000	0.000	0.000	0.00%	100.00%

Larval Mortality Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	0.00%
0	N	36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
8.8		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
25		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	0.00%
68		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
210		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
630		36	1.000	1.000	1.000	1.000	1.000	0.000	0.000	0.00%	100.00%

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Day 15 Mortality Detail

Conc-µg ai/g	Code	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
0	S	0.000	1.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0	N	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
8.8		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
25		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
68		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
210		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	1.000	0.000	0.000	0.000	1.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
630		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000				

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Larval Mortality Detail

Conc-µg ai/g	Code	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
0	S	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0	N	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
8.8		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
25		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
68		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
210		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
630		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000				

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study — **Smithers Viscient**

Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Sample ID:	17-2514-5005	**Code:**	50451002 dc2	**Project:**	Fungicide
Sample Date:	09 Jun-17	**Material:**	Ipconazole	**Source:**	Kureha Corporation
Receipt Date:	28 Jun-17	**CAS (PC):**		**Station:**	
Sample Age:	n/a	**Client:**	CDM Smith		

125618 50451002, mean-measured diet concentrations (ug ai/g diet), emergence and bee weight data, stats performed by A. Graff

SIngle Comparison Summary

Analysis ID	Endpoint	Comparison Method	P-Value	Comparison Result	S
17-0947-4374	Adult Emergence Rate	Fisher Exact Test	0.4290	Solvent Blank passed adult emergence rat	1

Multiple Comparison Summary

Analysis ID	Endpoint	Comparison Method	✓	NOEL	LOEL	TOEL	TU	PMSD	S
02-0038-9439	Adult Emergence Rate	Fisher Exact/Bonferroni-Holm Test		210	630	363.7		n/a	1
10-2022-3770	Emerged Bee Weight	Jonckheere-Terpstra Step-Down Test		210	>210	n/a		n/a	1

Point Estimate Summary

Analysis ID	Endpoint	Point Estimate Method	✓	Level	µg ai/g	95% LCL	95% UCL	TU	S
07-7337-8053	Adult Emergence Rate	GLM: Log-Normal (Probit)		EC1	15.8	n/a	n/a		1
				EC5	35.9	n/a	n/a		
				EC10	55.4	n/a	n/a		
				EC15	74.4	n/a	n/a		
				EC20	94	n/a	n/a		
				EC25	115	n/a	n/a		
				EC40	190	n/a	n/a		
			✓	EC50	258	n/a	n/a		
00-0921-7356	Adult Emergence Rate	Spearman-Kärber		EC50	313	275	357		1

Adult Emergence Rate Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	1	0.861			0.861	0.861	0.000	0.000	0.00%	0.00%
0	N	1	0.944			0.944	0.944	0.000	0.000	0.00%	-9.68%
8.8		1	0.944			0.944	0.944	0.000	0.000	0.00%	-9.68%
25		1	0.972			0.972	0.972	0.000	0.000	0.00%	-12.90%
68		1	0.917			0.917	0.917	0.000	0.000	0.00%	-6.45%
210		1	0.861			0.861	0.861	0.000	0.000	0.00%	0.00%
630		1	0.000			0.000	0.000	0.000	0.000		100.00%

Emerged Bee Weight Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	1	0.103			0.103	0.103	0	0	0.00%	0.00%
0	N	1	0.104			0.104	0.104	0	0	0.00%	-1.26%
8.8		1	0.101			0.101	0.101	0	0	0.00%	1.65%
25		1	0.103			0.103	0.103	0	0	0.00%	0.29%
68		1	0.1			0.1	0.1	0	0	0.00%	2.91%
210		1	0.101			0.101	0.101	0	0	0.00%	2.23%

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Adult Emergence Rate Detail

Conc-µg ai/g	Code	Rep 1
0	S	0.861
0	N	0.944
8.8		0.944
25		0.972
68		0.917
210		0.861
630		0.000

Emerged Bee Weight Detail

Conc-µg ai/g	Code	Rep 1
0	S	0.103
0	N	0.104
8.8		0.101
25		0.103
68		0.1
210		0.101
630		

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Batch ID:	03-8153-6585	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24
Sample ID:	08-0674-4220	**Code:**	50451002 dd	**Project:**	Fungicide
Sample Date:	09 Jun-17	**Material:**	Ipconazole	**Source:**	Kureha Corporation
Receipt Date:	28 Jun-17	**CAS (PC):**		**Station:**	
Sample Age:	n/a	**Client:**	CDM Smith		

125618 50451002, measured daily dietary doses (ug ai/larva/day), larval and d15 mortality, stats performed by A. Graff

Point Estimate Summary

Analysis ID	Endpoint	Point Estimate Method	✓	Level	µg/larv/da	95% LCL	95% UCL	TU	S
06-6192-6801	Day 15 Mortality	Trimmed Spearman-Kärber	✓	LC50	13.3	12	14.8		1
09-8870-1578	Larval Mortality	Spearman-Kärber		LC50	14.2	13.3	15		1

Day 15 Mortality Summary

Conc-µg/larv/da	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	36	0.111	0.003	0.219	0.000	1.000	0.053	0.319	286.85%	0.00%
0	N	36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
0.35		36	0.056	0.000	0.134	0.000	1.000	0.039	0.232	418.16%	-6.25%
1		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
2.8		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	-9.38%
8.5		36	0.111	0.003	0.219	0.000	1.000	0.053	0.319	286.85%	0.00%
25		36	1.000	1.000	1.000	1.000	1.000	0.000	0.000	0.00%	100.00%

Larval Mortality Summary

Conc-µg/larv/da	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	0.00%
0	N	36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
0.35		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
1		36	0.028	0.000	0.084	0.000	1.000	0.028	0.167	600.00%	0.00%
2.8		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
8.5		36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%
25		36	1.000	1.000	1.000	1.000	1.000	0.000	0.000	0.00%	100.00%

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Day 15 Mortality Detail

Conc-µg/larv/da	Code	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
0	S	0.000	1.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0	N	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0.35		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
1		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
2.8		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
8.5		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	1.000	0.000	0.000	0.000	1.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	1.000	0.000	0.000	1.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
25		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000				

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Larval Mortality Detail

Conc-µg/larv/da	Code	Rep 1	Rep 2	Rep 3	Rep 4	Rep 5	Rep 6	Rep 7	Rep 8	Rep 9	Rep 10
0	S	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0	N	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
0.35		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
1		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	1.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
2.8		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
8.5		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
		0.000	0.000	0.000	0.000	0.000	0.000				
25		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
		1.000	1.000	1.000	1.000	1.000	1.000				

CETIS Summary Report

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Batch ID:	13-0098-8894	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24
Sample ID:	11-1300-1312	**Code:**	50451002 dd2	**Project:**	Fungicide
Sample Date:	09 Jun-17	**Material:**	Ipconazole	**Source:**	Kureha Corporation
Receipt Date:	28 Jun-17	**CAS (PC):**		**Station:**	
Sample Age:	n/a	**Client:**	CDM Smith		

125618 50451002, measured daily dietary does (ug ai/larva/day), emergence and bee weight data, stats performed by A. Graff

Point Estimate Summary

Analysis ID	Endpoint	Point Estimate Method	✓	Level	µg/larv/da	95% LCL	95% UCL	TU	S
19-3170-0600	Adult Emergence Rate	GLM: Log-Normal (Probit)		EC1	0.636	n/a	n/a		1
				EC5	1.44	n/a	n/a		
				EC10	2.23	n/a	n/a		
				EC15	3	n/a	n/a		
				EC20	3.79	n/a	n/a		
				EC25	4.63	n/a	n/a		
				EC40	7.68	n/a	n/a		
			✓	EC50	10.4	n/a	n/a		
03-8851-2540	Adult Emergence Rate	Spearman-Kärber		EC50	12.6	11.1	14.3		1

Adult Emergence Rate Summary

Conc-µg/larv/da	Code	Count	Mean	95% LCL	95% UCL	Min	Max	Std Err	Std Dev	CV%	%Effect
0	S	1	0.861			0.861	0.861	0.000	0.000	0.00%	0.00%
0	N	1	0.944			0.944	0.944	0.000	0.000	0.00%	-9.68%
0.35		1	0.944			0.944	0.944	0.000	0.000	0.00%	-9.68%
1		1	0.972			0.972	0.972	0.000	0.000	0.00%	-12.90%
2.8		1	0.917			0.917	0.917	0.000	0.000	0.00%	-6.45%
8.5		1	0.861			0.861	0.861	0.000	0.000	0.00%	0.00%
25		1	0.000			0.000	0.000	0.000	0.000		100.00%

Adult Emergence Rate Detail

Conc-µg/larv/da	Code	Rep 1
0	S	0.861
0	N	0.944
0.35		0.944
1		0.972
2.8		0.917
8.5		0.861
25		0.000

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study — **Smithers Viscient**

Analysis ID:	02-8790-3949	**Endpoint:**	Day 15 Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:59	**Analysis:**	Parametric-Two Sample	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	Comparison Result	PMSD
Untransformed	C <> T	Solvent Blank passed day 15 mortality	12.30%

Equal Variance t Two-Sample Test

Control	vs	Control II	Test Stat	Critical	MSD	DF	P-Type	P-Value	Decision(α:5%)
Negative Control		Solvent Blank	1.39	1.99	0.12	70	CDF	0.1689	Non-Significant Effect

ANOVA Table

Source	Sum Squares	Mean Square	DF	F Stat	P-Value	Decision(α:5%)
Between	0.125	0.125	1	1.93	0.1689	Non-Significant Effect
Error	4.52778	0.0646825	70			
Total	4.65278		71			

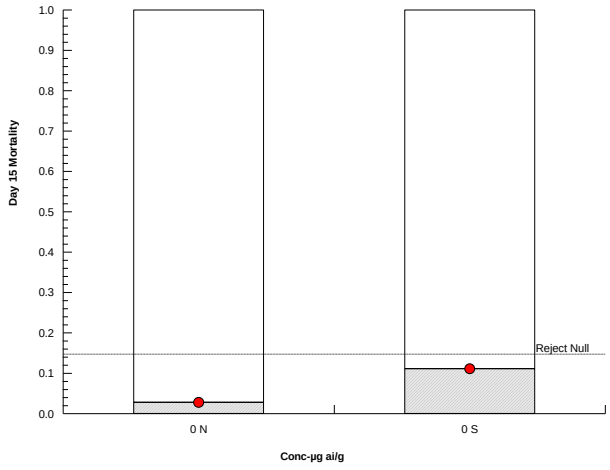
ANOVA Assumptions Tests

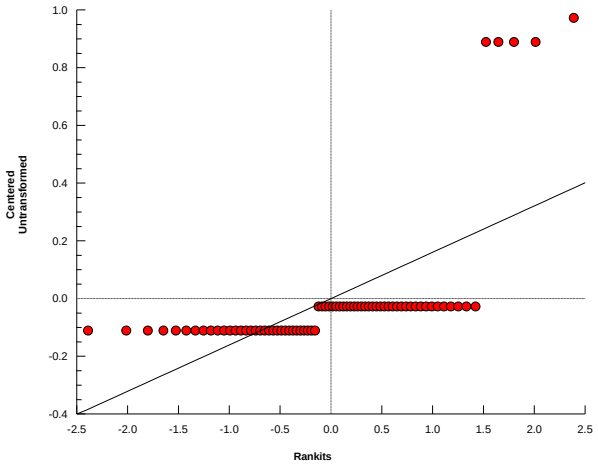
Attribute	Test	Test Stat	Critical	P-Value	Decision(α:1%)
Variance	Variance Ratio F Test	3.66	2.44	2.3E-04	Unequal Variances
Distribution	Shapiro-Wilk W Normality Test	0.4	0.954	1.3E-15	Non-Normal Distribution

Day 15 Mortality Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Median	Min	Max	Std Err	CV%	%Effect
0	S	36	0.111	0.003	0.219	0.000	0.000	1.000	0.053	286.85%	0.00%
0	N	36	0.028	0.000	0.084	0.000	0.000	1.000	0.028	600.00%	-9.38%

Graphics





Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	01-4910-8732	**Endpoint:**	Larval Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:59	**Analysis:**	Parametric-Two Sample	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	Comparison Result	PMSD
Untransformed	C <> T	Solvent Blank passed larval mortality	5.54%

Equal Variance t Two-Sample Test

Control	vs	Control II	Test Stat	Critical	MSD	DF	P-Type	P-Value	Decision(α:5%)
Negative Control		Solvent Blank	1	1.99	0.055	70	CDF	0.3208	Non-Significant Effect

ANOVA Table

Source	Sum Squares	Mean Square	DF	F Stat	P-Value	Decision(α:5%)
Between	0.0138889	0.0138889	1	1	0.3208	Non-Significant Effect
Error	0.972222	0.0138889	70			
Total	0.986111		71			

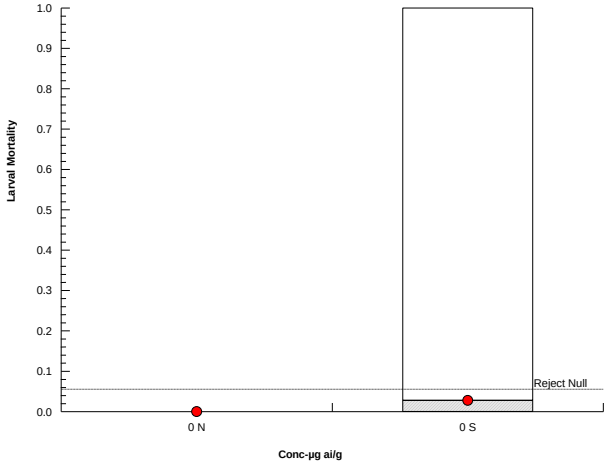
ANOVA Assumptions Tests

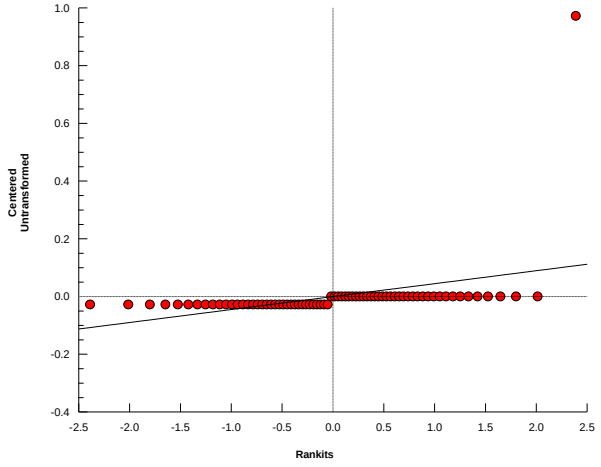
Attribute	Test	Test Stat	Critical	P-Value	Decision(α:1%)
Variance	Levene Equality of Variance Test	4.24	7.01	0.0432	Equal Variances
	Mod Levene Equality of Variance Test	1	7.01	0.3208	Equal Variances
Distribution	Shapiro-Wilk W Normality Test	0.159	0.954	2.7E-18	Non-Normal Distribution

Larval Mortality Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Median	Min	Max	Std Err	CV%	%Effect
0	S	36	0.028	0.000	0.084	0.000	0.000	1.000	0.028	600.00%	0.00%
0	N	36	0.000	0.000	0.000	0.000	0.000	0.000	0.000		-2.86%

Graphics





Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	07-6727-4899	**Endpoint:**	Day 15 Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:58	**Analysis:**	STP 2xK Contingency Tables	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	NOEL	LOEL	TOEL	TU
Untransformed	C < T	210	630	363.7	

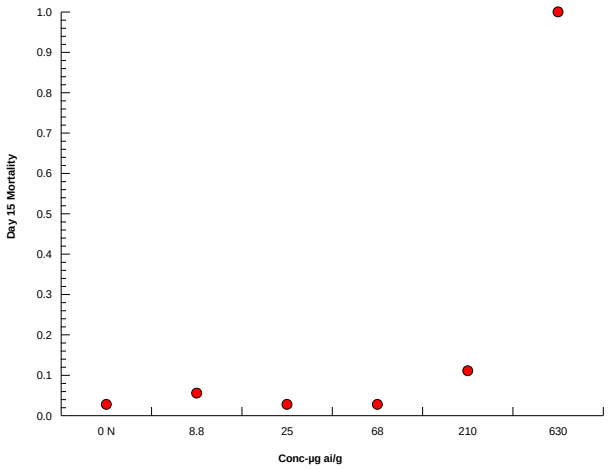
Fisher Exact/Bonferroni-Holm Test

Control	vs	Group	Test Stat	P-Type	P-Value	Decision(α:5%)
Negative Control		8.8	0.500	Exact	1.0000	Non-Significant Effect
		25	0.754	Exact	1.0000	Non-Significant Effect
		68	0.754	Exact	1.0000	Non-Significant Effect
		210	0.179	Exact	0.7140	Non-Significant Effect
		630*	0.000	Exact	4.2E-19	Significant Effect

Data Summary

Conc-µg ai/g	Code	NR	R	NR + R	Prop NR	Prop R	%Effect
0	N	35	1	36	0.972	0.0278	0.0%
8.8		34	2	36	0.944	0.0556	-100.0%
25		35	1	36	0.972	0.0278	0.0%
68		35	1	36	0.972	0.0278	0.0%
210		32	4	36	0.889	0.111	-300.0%
630		0	36	36	0	1	-3500.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	20-7378-5920	**Endpoint:**	Larval Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:58	**Analysis:**	STP 2xK Contingency Tables	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	NOEL	LOEL	TOEL	TU
Untransformed	C < T	210	630	363.7	

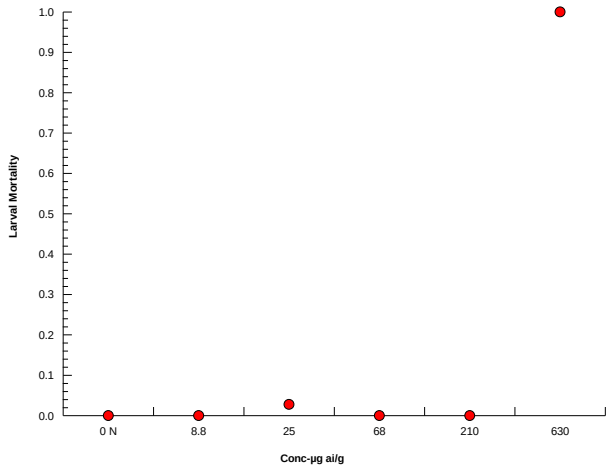
Fisher Exact/Bonferroni-Holm Test

Control	vs	Group	Test Stat	P-Type	P-Value	Decision(α:5%)
Negative Control		8.8	1.000	Exact	1.0000	Non-Significant Effect
		25	0.500	Exact	1.0000	Non-Significant Effect
		68	1.000	Exact	1.0000	Non-Significant Effect
		210	1.000	Exact	1.0000	Non-Significant Effect
		630*	0.000	Exact	1.1E-20	Significant Effect

Data Summary

Conc-µg ai/g	Code	NR	R	NR + R	Prop NR	Prop R	%Effect
0	N	36	0	36	1	0	
8.8		36	0	36	1	0	
25		35	1	36	0.972	0.0278	
68		36	0	36	1	0	
210		36	0	36	1	0	
630		0	36	36	0	1	

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

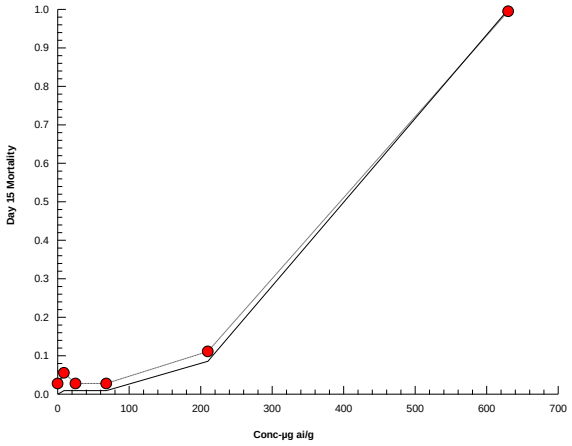
Analysis ID:	09-9507-1814	**Endpoint:**	Day 15 Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:59	**Analysis:**	Trimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Trimmed Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	LC50	95% LCL	95% UCL
Control Threshold	0.0278	0.95%	2.52	0.0233	332	298	370

Day 15 Mortality Summary			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg ai/g	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.0278	0.0%
8.8		36	0.056	0.000	1.000	0.232	418.00%	2.86%	2/36	0.037	0.95%
25		36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.037	0.95%
68		36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.037	0.95%
210		36	0.111	0.000	1.000	0.319	287.00%	8.57%	4/36	0.111	8.57%
630		36	1.000	1.000	1.000	0.000	0.00%	100.0%	36/36	1	100.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

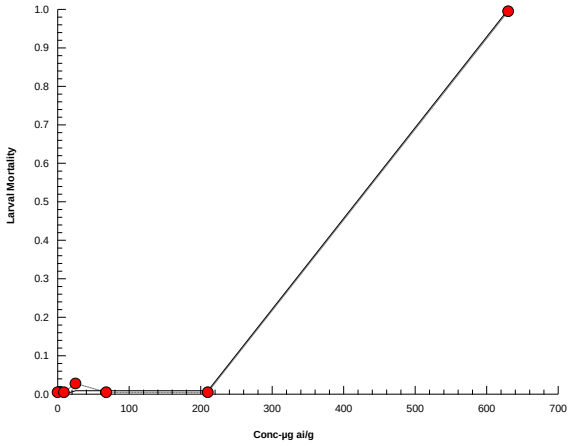
Analysis ID:	18-7051-1920	**Endpoint:**	Larval Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 13:59	**Analysis:**	Untrimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	18-4129-6219	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	LC50	95% LCL	95% UCL
Control Threshold	0	0.00%	2.55	0.0128	353	333	375

Larval Mortality Summary			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg ai/g	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	36	0.000	0.000	0.000	0.000		0.0%	0/36	0	0.0%
8.8		36	0.000	0.000	0.000	0.000		0.0%	0/36	0	0.0%
25		36	0.028	0.000	1.000	0.167	600.00%	2.78%	1/36	0.00926	0.93%
68		36	0.000	0.000	0.000	0.000		0.0%	0/36	0.00926	0.93%
210		36	0.000	0.000	0.000	0.000		0.0%	0/36	0.00926	0.93%
630		36	1.000	1.000	1.000	0.000	0.00%	100.0%	36/36	1	100.0%

Graphics



CETIS Analytical Report

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	10-2022-3770	**Endpoint:**	Emerged Bee Weight	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 14:56	**Analysis:**	Nonparametric-Control vs Ord. Treatments	**Status Level:**	1
Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	NOEL	LOEL	TOEL	TU
Untransformed	C > T	210	>210	n/a	

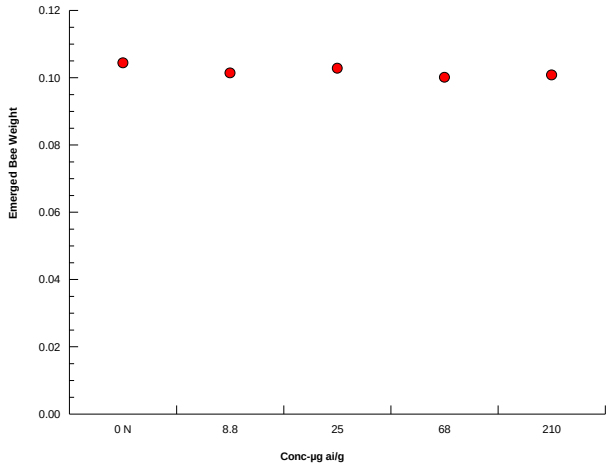
Jonckheere-Terpstra Step-Down Test

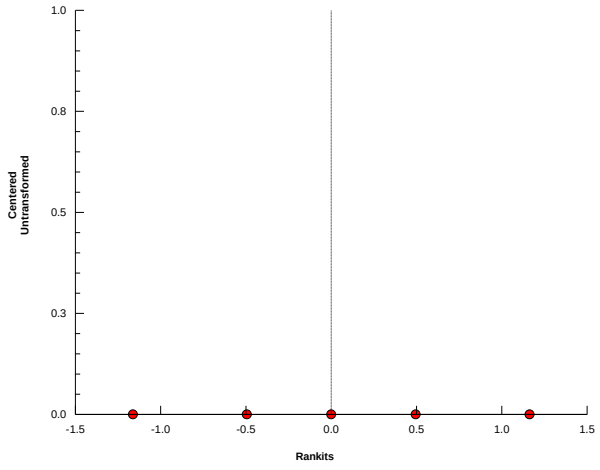
Control	vs	Conc-µg ai/g	Test Stat	Critical	P-Type	P-Value	Decision(α:5%)
Negative Control		8.8	1	n/a	Exact	0.5000	Non-Significant Effect
		25	2	n/a	Exact	0.5000	Non-Significant Effect
		68	5	n/a	Exact	0.1667	Non-Significant Effect
		210	8	n/a	Exact	0.1167	Non-Significant Effect

Emerged Bee Weight Summary

Conc-µg ai/g	Code	Count	Mean	95% LCL	95% UCL	Median	Min	Max	Std Err	CV%	%Effect
0	N	1	0.104			0.104	0.104	0.104	0	0.00%	0.00%
8.8		1	0.101			0.101	0.101	0.101	0	0.00%	2.87%
25		1	0.103			0.103	0.103	0.103	0	0.00%	1.53%
68		1	0.1			0.1	0.1	0.1	0	0.00%	4.12%
210		1	0.101			0.101	0.101	0.101	0	0.00%	3.45%

Graphics





Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	02-0038-9439	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 14:56	**Analysis:**	STP 2xK Contingency Tables	**Status Level:**	1
Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	NOEL	LOEL	TOEL	TU
Untransformed	C > T	210	630	363.7	

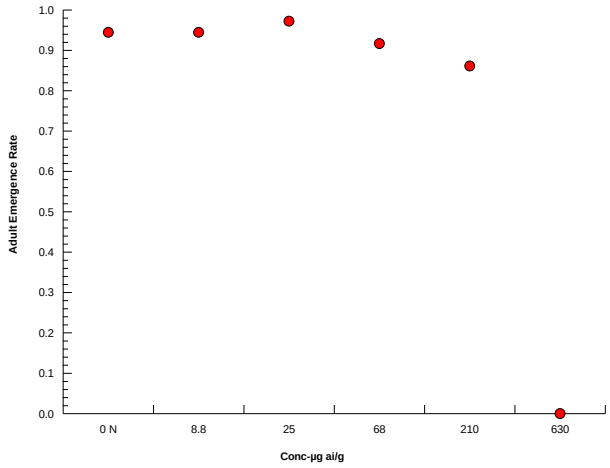
Fisher Exact/Bonferroni-Holm Test

Control	vs	Group	Test Stat	P-Type	P-Value	Decision(α:5%)
Negative Control		8.8	0.693	Exact	1.0000	Non-Significant Effect
		25	0.880	Exact	0.8803	Non-Significant Effect
		68	0.500	Exact	1.0000	Non-Significant Effect
		210	0.214	Exact	0.8580	Non-Significant Effect
		630*	0.000	Exact	7.9E-18	Significant Effect

Data Summary

Conc-µg ai/g	Code	NR	R	NR + R	Prop NR	Prop R	%Effect
0	N	34	2	36	0.944	0.0556	0.0%
8.8		34	2	36	0.944	0.0556	0.0%
25		35	1	36	0.972	0.0278	-2.94%
68		33	3	36	0.917	0.0833	2.94%
210		31	5	36	0.861	0.139	8.82%
630		0	36	36	0	1	100.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	17-0947-4374	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:46	**Analysis:**	Single 2x2 Contingency Table	**Status Level:**	1
Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Data Transform	Alt Hyp	Comparison Result
Untransformed	C <> T	Solvent Blank passed adult emergence rate

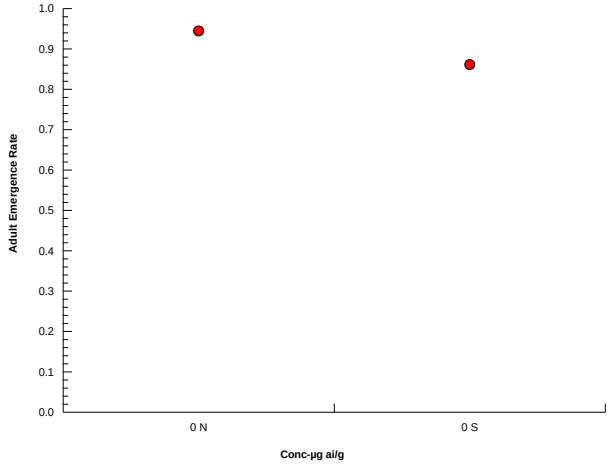
Fisher Exact Test

Control	vs	Control	Test Stat	P-Type	P-Value	Decision(α:5%)
Negative Control		Solvent Blank	0.429	Exact	0.4290	Non-Significant Effect

Data Summary

Conc-µg ai/g	Code	NR	R	NR + R	Prop NR	Prop R	%Effect
0	S	31	5	36	0.861	0.139	8.82%
0	N	34	2	36	0.944	0.0556	0.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study — **Smithers Viscient**

Analysis ID:	07-7337-8053	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 14:57	**Analysis:**	Linear Regression (GLM)	**Status Level:**	1
Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Linear Regression Options

Model Name	Link Function	Threshold Option	Thresh	Optimize	Pooled	Het Corr	Weighted
Log-Normal (Probit)	η=inv Φ[π]	Zero Threshold	0	No	No	Yes	Yes

Regression Summary

Iters	LL	AICc	BIC	Mu	Sigma	Adj R2	PMSD	F Stat	P-Value	Decision(α:5%)
10	-26.8	63.5	56.8	2.41	0.521	0.99				Lack of Fit Not Tested

Point Estimates

Level	µg ai/g	95% LCL	95% UCL
EC1	15.8	n/a	n/a
EC5	35.9	n/a	n/a
EC10	55.4	n/a	n/a
EC15	74.4	n/a	n/a
EC20	94	n/a	n/a
EC25	115	n/a	n/a
EC40	190	n/a	n/a
EC50	258	n/a	n/a

Regression Parameters

Parameter	Estimate	Std Error	95% LCL	95% UCL	t Stat	P-Value	Decision(α:5%)
Intercept	-4.63	2.94	-14	4.73	-1.57	0.2136	Non-Significant Parameter
Slope	1.92	1.28	-2.14	5.98	1.5	0.2298	Non-Significant Parameter

ANOVA Table

Source	Sum Squares	Mean Square	DF	F Stat	P-Value	Decision(α:5%)
Model	8520	8520	1	388	2.9E-04	Significant
Residual	65.9	22	3			

Residual Analysis

Attribute	Method	Test Stat	Critical	P-Value	Decision(α:5%)
Model Fit	Likelihood Ratio GOF Test	42.8	7.81	<1.0E-37	Significant Heterogeneity
	Pearson Chi-Sq GOF Test	65.9	7.81	<1.0E-37	Significant Heterogeneity
Distribution	Shapiro-Wilk W Normality Test	0.976	0.34	0.9122	Normal Distribution

Adult Emergence Rate Summary — **Calculated Variate(A/B)**

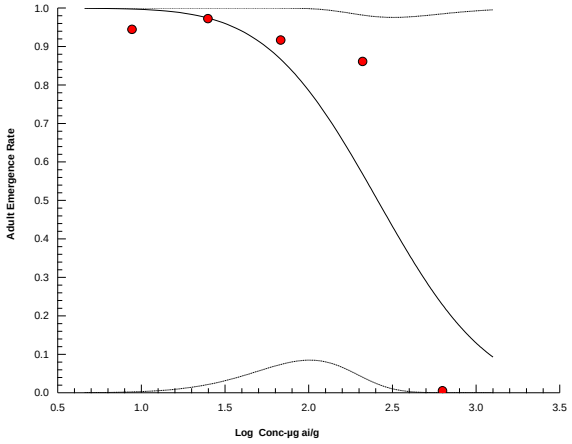
Conc-µg ai/g	Code	Count	Mean	Min	Max	Std Err	Std Dev	CV%	%Effect	A	B
8.8		1	0.944	0.944	0.944	0.000	0.000	0.00%	0.0%	34	36
25		1	0.972	0.972	0.972	0.000	0.000	0.00%	-2.94%	35	36
68		1	0.917	0.917	0.917	0.000	0.000	0.00%	2.94%	33	36
210		1	0.861	0.861	0.861	0.000	0.000	0.00%	8.82%	31	36
630		1	0.000	0.000	0.000	0.000	0.000		100.0%	0	36

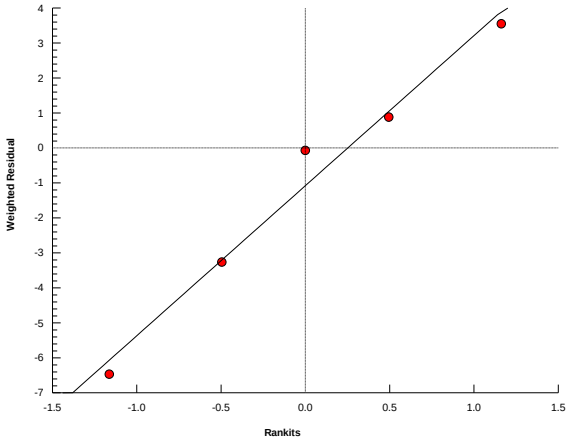
Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

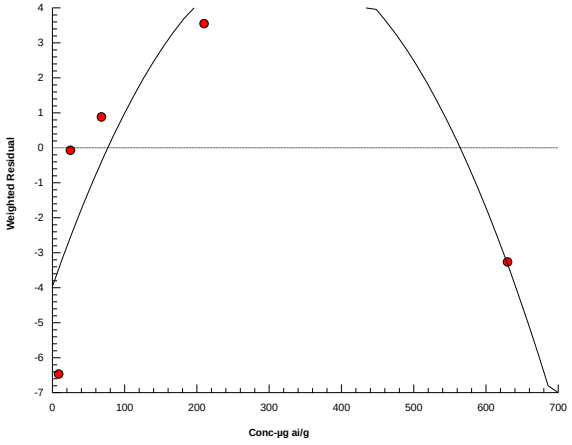
Analysis ID:	07-7337-8053	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 14:57	**Analysis:**	Linear Regression (GLM)	**Status Level:**	1

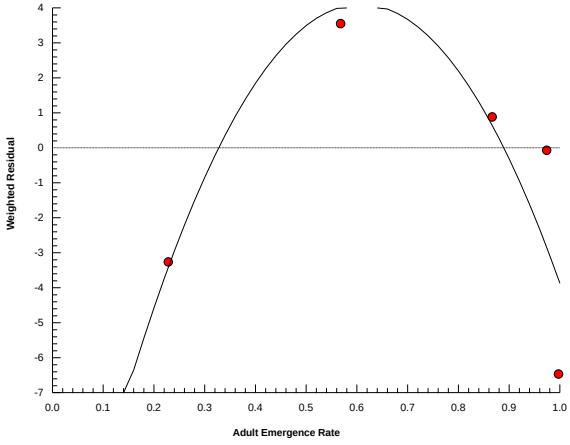
Graphics

Log-Normal: inv Φ[π]=α+β·log[x]









CETIS Analytical Report

Test Code/ID: 50451002 dc2 / 12-7549-8092

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study — **Smithers Viscient**

Analysis ID:	00-0921-7356	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 14:57	**Analysis:**	Untrimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	07-1149-6742	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

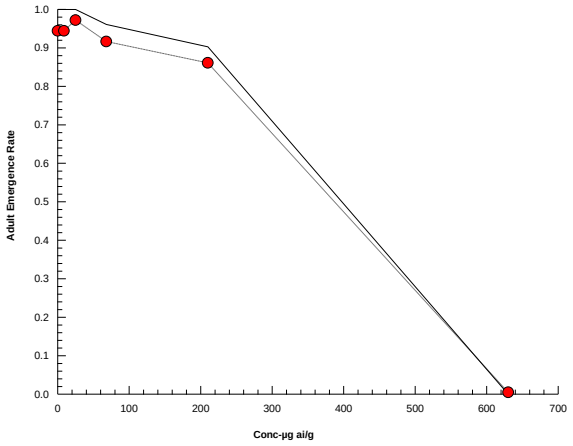
Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	EC50	95% LCL	95% UCL
Control Threshold	0.0556	0.00%	2.5	0.0281	313	275	357

Adult Emergence Rate Summary

			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg ai/g	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	1	0.944	0.944	0.944	0.000	0.00%	0.0%	34/36	0.954	0.0%
8.8		1	0.944	0.944	0.944	0.000	0.00%	0.0%	34/36	0.954	0.0%
25		1	0.972	0.972	0.972	0.000	0.00%	-2.94%	35/36	0.954	0.0%
68		1	0.917	0.917	0.917	0.000	0.00%	2.94%	33/36	0.917	3.88%
210		1	0.861	0.861	0.861	0.000	0.00%	8.82%	31/36	0.861	9.71%
630		1	0.000	0.000	0.000	0.000		100.0%	0/36	0	100.0%

Graphics



CETIS Analytical Report

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

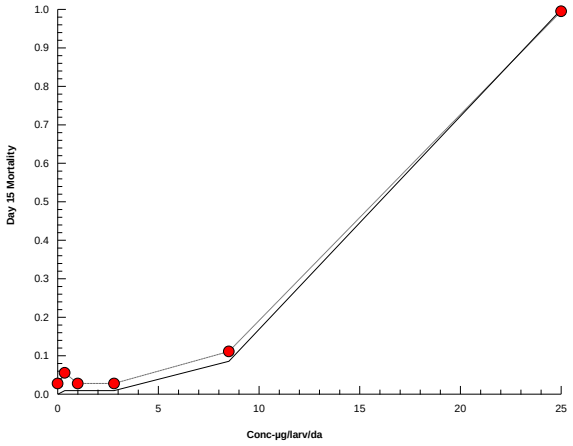
Analysis ID:	06-6192-6801	**Endpoint:**	Day 15 Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:22	**Analysis:**	Trimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	03-8153-6585	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Trimmed Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	LC50	95% LCL	95% UCL
Control Threshold	0.0278	0.95%	1.12	0.023	13.3	12	14.8

Day 15 Mortality Summary			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg/larv/da	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.0278	0.0%
0.35		36	0.056	0.000	1.000	0.232	418.00%	2.86%	2/36	0.037	0.95%
1		36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.037	0.95%
2.8		36	0.028	0.000	1.000	0.167	600.00%	0.0%	1/36	0.037	0.95%
8.5		36	0.111	0.000	1.000	0.319	287.00%	8.57%	4/36	0.111	8.57%
25		36	1.000	1.000	1.000	0.000	0.00%	100.0%	36/36	1	100.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

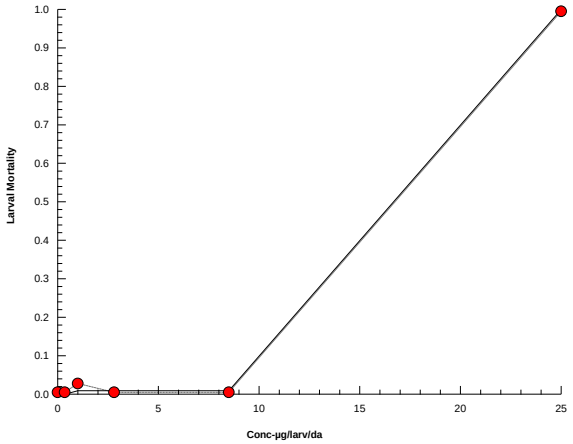
Analysis ID:	09-8870-1578	**Endpoint:**	Larval Mortality	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:22	**Analysis:**	Untrimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	03-8153-6585	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	LC50	95% LCL	95% UCL
Control Threshold	0	0.00%	1.15	0.0128	14.2	13.3	15

Larval Mortality Summary			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg/larv/da	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	36	0.000	0.000	0.000	0.000		0.0%	0/36	0	0.0%
0.35		36	0.000	0.000	0.000	0.000		0.0%	0/36	0	0.0%
1		36	0.028	0.000	1.000	0.167	600.00%	2.78%	1/36	0.00926	0.93%
2.8		36	0.000	0.000	0.000	0.000		0.0%	0/36	0.00926	0.93%
8.5		36	0.000	0.000	0.000	0.000		0.0%	0/36	0.00926	0.93%
25		36	1.000	1.000	1.000	0.000	0.00%	100.0%	36/36	1	100.0%

Graphics



Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	19-3170-0600	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:25	**Analysis:**	Linear Regression (GLM)	**Status Level:**	1
Batch ID:	13-0098-8894	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Linear Regression Options

Model Name	Link Function	Threshold Option	Thresh	Optimize	Pooled	Het Corr	Weighted
Log-Normal (Probit)	η=inv Φ[π]	Zero Threshold	0	No	No	Yes	Yes

Regression Summary

Iters	LL	AICc	BIC	Mu	Sigma	Adj R2	PMSD	F Stat	P-Value	Decision(α:5%)
10	-27.1	64.3	57.5	1.02	0.522	0.99				Lack of Fit Not Tested

Point Estimates

Level	µg/larv/da	95% LCL	95% UCL
EC1	0.636	n/a	n/a
EC5	1.44	n/a	n/a
EC10	2.23	n/a	n/a
EC15	3	n/a	n/a
EC20	3.79	n/a	n/a
EC25	4.63	n/a	n/a
EC40	7.68	n/a	n/a
EC50	10.4	n/a	n/a

Regression Parameters

Parameter	Estimate	Std Error	95% LCL	95% UCL	t Stat	P-Value	Decision(α:5%)
Intercept	-1.95	1.27	-6	2.1	-1.53	0.2229	Non-Significant Parameter
Slope	1.92	1.3	-2.22	6.05	1.47	0.2370	Non-Significant Parameter

ANOVA Table

Source	Sum Squares	Mean Square	DF	F Stat	P-Value	Decision(α:5%)
Model	8740	8740	1	389	2.8E-04	Significant
Residual	67.4	22.5	3			

Residual Analysis

Attribute	Method	Test Stat	Critical	P-Value	Decision(α:5%)
Model Fit	Likelihood Ratio GOF Test	43.5	7.81	<1.0E-37	Significant Heterogeneity
	Pearson Chi-Sq GOF Test	67.4	7.81	<1.0E-37	Significant Heterogeneity
Distribution	Shapiro-Wilk W Normality Test	0.975	0.34	0.9089	Normal Distribution

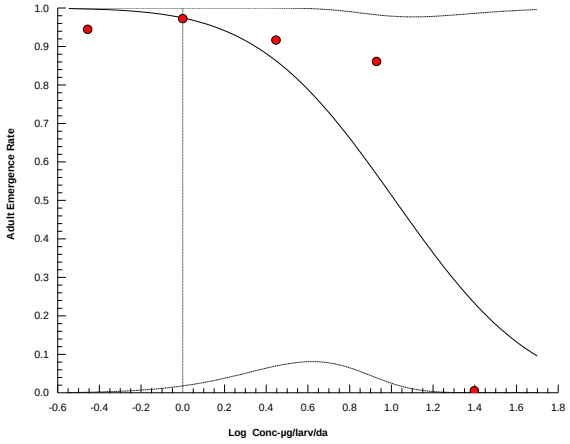
Adult Emergence Rate Summary **Calculated Variate(A/B)**

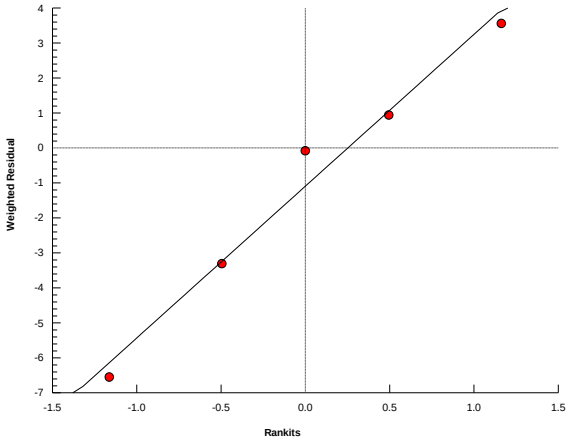
Conc-µg/larv/da	Code	Count	Mean	Min	Max	Std Err	Std Dev	CV%	%Effect	A	B
0.35		1	0.944	0.944	0.944	0.000	0.000	0.00%	0.0%	34	36
1		1	0.972	0.972	0.972	0.000	0.000	0.00%	-2.94%	35	36
2.8		1	0.917	0.917	0.917	0.000	0.000	0.00%	2.94%	33	36
8.5		1	0.861	0.861	0.861	0.000	0.000	0.00%	8.82%	31	36
25		1	0.000	0.000	0.000	0.000	0.000		100.0%	0	36

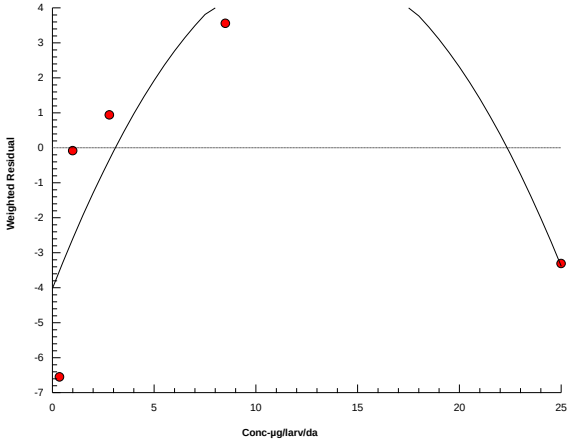
Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

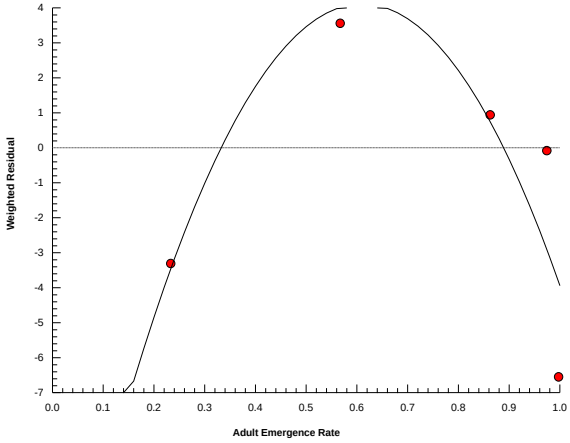
Analysis ID:	19-3170-0600	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:25	**Analysis:**	Linear Regression (GLM)	**Status Level:**	1

Graphics Log-Normal: inv Φ[π]=α+β·log[x]









CETIS Analytical Report

Test Code/ID: 50451002 dd2 / 10-6855-4371

Special Study Honey bee Larval Chronic Oral Toxicity, 21-day Study **Smithers Viscient**

Analysis ID:	03-8851-2540	**Endpoint:**	Adult Emergence Rate	**CETIS Version:**	CETISv1.9.5
Analyzed:	13 May-19 15:25	**Analysis:**	Untrimmed Spearman-Kärber	**Status Level:**	1
Batch ID:	13-0098-8894	**Test Type:**	OECD 2014 HB Larval Repeat Exp	**Analyst:**	
Start Date:	09 Jun-17	**Protocol:**	Larval Chronic Oral Toxicity, 21-day Study	**Diluent:**	
Ending Date:	28 Jun-17	**Species:**	Apis mellifera	**Brine:**	
Test Length:	19d 0h	**Taxon:**		**Source:**	Wood's Beekeeping Supply, **Age:** <24

Spearman-Kärber Estimates

Threshold Option	Threshold	Trim	Mu	Sigma	EC50	95% LCL	95% UCL
Control Threshold	0.0556	0.00%	1.1	0.0278	12.6	11.1	14.3

Adult Emergence Rate Summary			Calculated Variate(A/B)							Isotonic Variate	
Conc-µg/larv/da	**Code**	**Count**	**Mean**	**Min**	**Max**	**Std Dev**	**CV%**	**%Effect**	**A/B**	**Mean**	**%Effect**
0	N	1	0.944	0.944	0.944	0.000	0.00%	0.0%	34/36	0.954	0.0%
0.35		1	0.944	0.944	0.944	0.000	0.00%	0.0%	34/36	0.954	0.0%
1		1	0.972	0.972	0.972	0.000	0.00%	-2.94%	35/36	0.954	0.0%
2.8		1	0.917	0.917	0.917	0.000	0.00%	2.94%	33/36	0.917	3.88%
8.5		1	0.861	0.861	0.861	0.000	0.00%	8.82%	31/36	0.861	9.71%
25		1	0.000	0.000	0.000	0.000		100.0%	0/36	0	100.0%

Graphics